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Etiology of Cancer Associated Thromboembolism (CAT), and Diet, Lifestyle and Medicine to Reduce Cancer and Venous Thromboembolism

Kenji Yokoyama

Abstract

Cancer is one of the leading causes of death in developed countries, and cancer patients often develop venous thromboembolism (VTE). VTE is the second leading cause of death in cancer patients receiving chemotherapy. The incidence of VTE varies among cancers, and it is highest in pancreatic cancer patients. Increased white blood cells and thrombocytosis are risk factors for developing cancer-associated VTE. Some other proteins (tissue factor, podoplanin, P-selectin, and plasminogen activator inhibitor-1) may also play roles in thrombus formation in cancer patients. Certain diets and nutrition (e.g., enough fish, vegetables, and fruits) may reduce the risk of VTE. Certain diets and nutrition also may reduce the risk of cancer, and alcohol drinking and cigarette smoking definitely increase risk of cancer. Some studies suggest that aspirin, a widely used antiplatelet drug, may reduce cancer incidence and mortality, but other studies fail to show the beneficial effects of aspirin.

Keywords: cancer, venous thromboembolism, fish, vegetables, aspirin

1. Introduction

Cancer is one of the leading causes of death in developed countries including Japan. According to the Japanese Cancer Institute registry data, 1,017,200 patients were estimated to be newly diagnosed with cancer, and 380,300 patients were estimated to die from cancer in 2019 [1]. Colon cancer is the most often diagnosed in Japanese people, followed by gastric and lung cancer. Lung cancer most often causes death related to cancer, followed by colon and gastric cancer. Approximately half of Japanese people suffer from cancer during their lifetime, and one-third die from cancer. Venous thromboembolism (VTE) is a common and serious complication in patients with cancer. The risk of VTE in cancer patients is severalfold higher than that in individuals without cancer [2, 3], and VTE is the second leading cause

of death in cancer patients undergoing chemotherapy after death directly related to cancer [4]. Therefore, it is important to prevent and treat cancer-associated VTE to improve prognosis of cancer.

2. History of cancer-associated thrombosis

French physician Armand Trousseau first described the relationship between cancer and thrombosis when he reported multiple cancer patients complicated with “phlegmasia alba dolens” caused by deep vein thrombosis in 1865 [5]. He speculated that excess of fibrin and hypercoagulable state of blood caused thrombosis in these patients. Two years later, he suffered from “phlegmasia alba dolens,” and he died from gastric cancer. Since then, many studies have revealed the relationships between cancer and thrombosis. Presently, it is well known that thrombosis, i.e., venous thromboembolism (VTE), arterial thrombosis, disseminated intravascular coagulation, and thrombotic microangiopathy, often occurs in cancer patients, and thrombosis occurring in cancer patients become to be recognized as cancer-associated thrombosis (CAT) (Table 1).

Venous thromboembolism
Arterial thrombosis
Disseminated intravascular coagulation
Thrombotic microangiopathy

Table 1.
Cancer-associated thrombosis.

3. Epidemiology and etiology of venous thromboembolism

Among CAT, VTE most often occurs in cancer patients. VTE is a disease that includes deep vein thrombosis (DVT), which usually occurs in the lower legs, and pulmonary embolisms (PE). Most isolated distal DVTs do not extend to the proximal veins and remain uneventful, whereas parts of clot may break off from proximal DVTs and they may cause potentially life-threatening PE. VTE is the third frequent cardiovascular diseases in Western countries next to myocardial infarction and stroke, and it is estimated that annual incidence of VTE is 1–2 per 1000 adults in the USA [6]. Racial differences may exist in the incidence of VTE, and it is reported that the incidence of VTE in whites is five times higher than that in Asians [7]. Previously, the incidence of VTE in Japanese population was supposed to be low, but more Japanese patients have been diagnosed with VTE, recently. The number of patients diagnosed with PE was 28 per 1,000,000 people in 1996, and it increased to 126 in 2011 [8].

There are several risk factors that induce VTE, and cancer is one of the main risk factors for VTE (Table 2). It has been reported that cancer is associated with 18% of all VTE, and the overall risk of VTE was increased sevenfold in patients with a malignancy (odds ratio [OR], 6.7; 95% confidence interval [CI], 5.2–8.6) vs. persons without malignancy [9].

Major surgery
Cancer
Pregnancy
Delivery
Acute medical illness
Paralysis
Prolonged bed rest
Oral contraceptive
Obesity
Elderly
Thrombophilia

Table 2.
Risk factors for venous thromboembolism.

4. Risk factors for cancer-associated venous thromboembolism

Incidence rates of VTE increase with age in the general population. Likewise, cancer-associated VTE occurs more often in the elderly population than younger population. Khorana et al. reported that age 65 or older is an independent risk factor for developing cancer-associated VTE. Cancer-associated VTE is more common in female sex and black race [3]. Obesity; complications such as respiratory disease, kidney disease, and infection; and poor performance status are also risk factors for cancer-associated VTE [10–12].

The risk of VTE varies by cancer site, and meta-analysis of several studies proves that the incidence of VTE is highest in the pancreatic cancer patients, followed by hematological malignancy and brain tumor patients [13]. VTE more often occurs in patients with advanced cancer than in patients with early cancer [14]. The incidence of VTE also varies by cancer histology, is higher in lung adenocarcinoma patients than in lung squamous cell carcinoma patients [15], and is higher in high-grade lymphoma patients than in low-grade lymphoma patients [16, 17].

Cancer treatment also affects VTE incidence. VTE is a common complication of surgery, regardless of whether it is cancer surgery or not, and adequate prophylaxis is recommended in guidelines including Japanese guideline [18]. However, among cancer patients who received adequate VTE prophylaxis after surgery, 2.1% of them developed massive VTE and 0.8% of them died [19]. Many types of anticancer drugs, such as cisplatin, l-asparaginase, and bevacizumab, also increase risk of thrombosis in cancer patients. Especially, the incidence of VTE is very high in multiple myeloma patients receiving immunomodulatory drugs (e.g., thalidomide, lenalidomide, and pomalidomide), and these patients need primary prevention of VTE by using antithrombotic drugs. Cancer patients often need indwelling central venous catheter (CVC) for delivery of intravenous drugs, parenteral nutrition, and collecting blood samples. Indwelling CVC increases risk of developing VTE, and it is estimated that the risk of symptomatic catheter thrombosis is 0.3–28% [20].

Considering these factors, several risk models to predict the occurrence of cancer-associated VTE have been published. Khorana score is the most widely used risk model among them [21]. Five predictive variables are identified in this score: site of cancer (2 points for very high-risk site, 1 point for high-risk site), platelet

count of $350 \times 10^9/L$ or more, hemoglobin less than 100 g/L (10 g/dL) and/or the use of erythropoiesis-stimulating agents, leukocyte count more than $11 \times 10^9/L$, and body mass index of 35 kg/m^2 or more (1 point each). Rates of VTE have been reported to be 0.3% in low-risk (score = 0), 2% in intermediate-risk (score = 1–2), and 6.7% in high-risk (score ≥ 3) category over a median of 2.5 months.

5. Pathogenesis of cancer-associated venous thromboembolism

Stasis of blood flow, hypercoagulability, and endothelial injury are known as Virchow's triad, and they are involved in thrombus formation. Stasis of blood flow caused by several factors, such as poor performance status, indwelling CVC, and venous compression by tumor, is thought to be involved in the pathogenesis of VTE in cancer patients.

Blood cells also play an important role in the occurrence of VTE in cancer patients. Leukocyte count $11 \times 10^9/L$ or above is a risk factor of VTE in cancer patients [21]. Increased leukocyte is found in 20–30% of cancer patients, and it is common in colon and lung cancer patients. Increased expression of granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, and interleukin-6 causes leukocyte increase in cancer patients [22, 23]. Neutrophils may enhance thrombosis through formation of neutrophil extracellular traps (NETs), which take in erythrocytes and platelets, and bind to tissue factor (TF) resulting in activation of coagulation [24, 25]. Increased incidences of VTE are reported both in cancer patients with thrombocytosis prior to cancer diagnosis and thrombocytosis at cancer diagnosis [11, 26, 27]. Higher expression of platelet factor 4, which activates platelets, in cancer patients may be related to the development of VTE [28, 29]. Platelets also play a regulatory role in NETs formation. These may play an important role in the pathogenesis of cancer-associated VTE.

Some proteins also have been reported to be involved in the pathogenesis of cancer-associated VTE. TF plays an important role in hemostasis and activates factor IX and factor X to initiate extrinsic coagulation pathway by forming a complex with factor VII or activated factor VII. VTE most frequently occurs in pancreatic cancer patients, and pancreatic cancer expresses TF. Expression levels of TF correlate with histologic grades of cancer, and the incidence of VTE is higher in patients with pancreatic cancer with high TF expression level [30, 31]. Podoplanin is a protein which activates platelets by binding to platelet C-type lectin receptor 2 (CLEC-2) [32, 33]. The relationships between podoplanin and VTE are proven in patients with glioblastoma multiforme (GBM). Expression levels of podoplanin vary by GBM subtype. GBM with high podoplanin expression level has a high number of platelet aggregates in tumor vessels and is reported to have high incidence of VTE [34].

P-selectin is a protein that exists in platelets and endothelial cells, and soluble form of P-selectin exists in plasma. P-selectin induces leukocytes to damaged endothelium for thrombus formation. The incidence of VTE is reported to be higher in cancer patients with high levels of soluble P-selectin [35]. Inhibition of P-selectin reduces thrombus formation in animal models [36].

Plasminogen activator inhibitor-1 (PAI-1) inhibits plasmin, which is synthesized from plasminogen to dissolve thrombus. Increased level of PAI-1 causes thrombotic tendency. The incidence of VTE is high in pancreatic cancer patients with increased levels of PAI-1 [37]. It is reported that administration of bevacizumab to mice transplanted with lung cancer cells increases PAI-1 expression and enlarges the size of thrombus. Administration of PAI-1 inhibitor to these mice decreases the thrombus size [38]. These findings suggest that increased PAI-1 may be related to the occurrence of cancer-associated VTE (**Figure 1**).

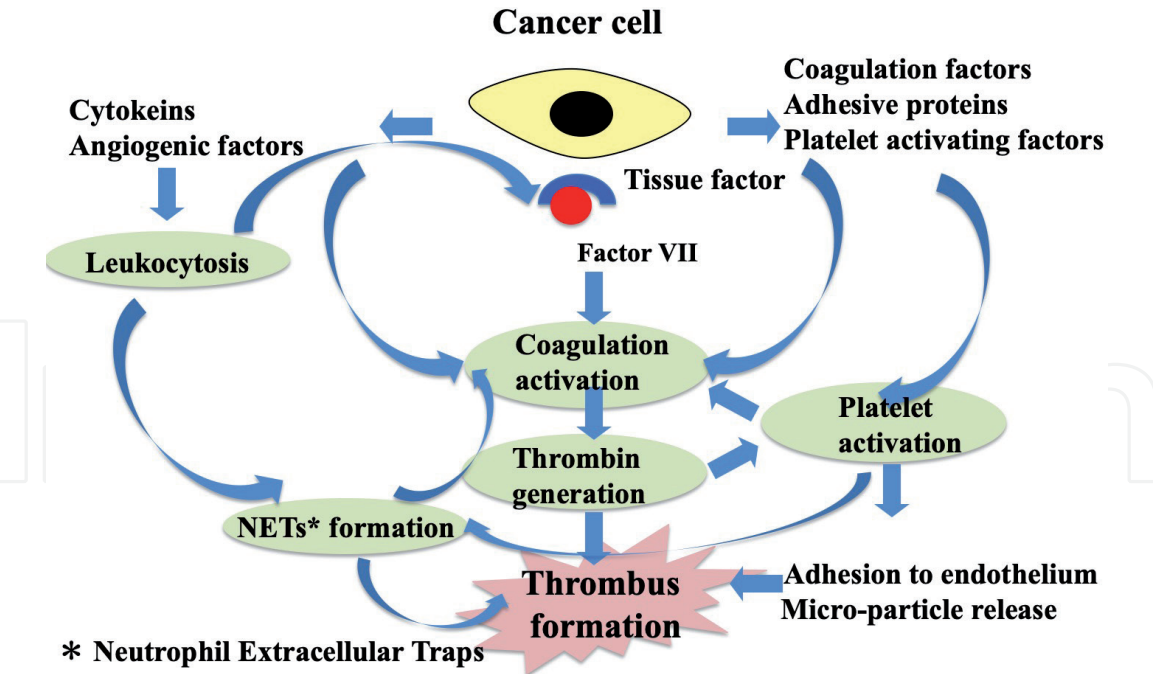


Figure 1.
Pathogenesis of cancer-associated venous thromboembolism. Cancer cells express and release various proteins. These induce leukocytosis and thrombocytosis and activate coagulation resulting in thrombus formation.

6. Diet, nutrition, and VTE

Considering the pathogenesis of cancer-associated VTE described in the previous section, it is unlikely that certain diets and nutrition can suppress the development of cancer-associated VTE specifically. Then, are there any diets and nutrition which may prevent the development of VTE in general, not just cancer-associated? The association between diet and nutrition and thrombosis has not necessarily been well analyzed for VTE, but it has been well analyzed for arterial thrombosis such as ischemic heart disease or cerebral infarction. In 2010, the American College of Cardiology announced seven lifestyles to reduce deaths caused by cardiovascular and cerebral infarction by 20% by 2020: (1) nonsmoking, (2) body mass index $<25 \text{ kg/m}^2$, (3) physical activity at goal levels, (4) pursuit of a diet consistent with the current guideline recommendations, (5) untreated total cholesterol $<200 \text{ mg/dL}$, (6) untreated blood pressure $<120/<80 \text{ mm Hg}$, and (7) fasting blood glucose $<100 \text{ mg/dL}$ [39]. Do these lifestyles also reduce the incidence of VTE? Hypertension, hypercholesterolemia, diabetes (these are related to diet and nutrition), and smoking are risk factors for atherosclerotic cardiovascular disease, and meta-analysis of nine clinical trials revealed that only smoking is a risk factor for VTE among them [40]. These results suggest that diets and nutrition to prevent arterial thrombosis are not necessarily effective for VTE prevention. On the other hand, obesity, one of the risk factors for arterial thrombosis, is also known to be one of the risk factors for the development of VTE. Analysis of the association between 95 BMI-related gene polymorphisms and VTE development proves that five of the polymorphisms are associated with VTE development [41]. Therefore, taking a diet without too much calories or carbohydrates to maintain proper body weight is considered to be useful for VTE prevention.

Other reports examining the relationship between diet and nutrition and VTE are as follow. The incidence of VTE is 22% lower for those who eat fish three or more times a week than for those who eat twice or less a week [42] and is low for those who eat enough fish, vegetables, and fruits and eat less red meat and processed meat [43]. These reports suggest that diets to prevent arterial

thrombosis might also be useful to prevent VTE. Furthermore, consumption of grape suppresses thrombin generation and enhances fibrinolysis [44]. Diets with 20, 30, and 50% of their calories on protein, lipids, and carbohydrates for 12 months result in reduction of abdominal circumference, increased HDL-C, decreased fibrinogen, and significantly increased interleukin-10 in those with metabolic syndrome [45]. These reports suggest that diet and nutrition might directly affect the blood coagulation and fibrinolysis which play an important role in the development of VTE.

Several reports related to the alcohol consumption and VTE have also been published. Women consuming alcohol daily were at 26% lower risk of VTE than non-consumers [46], and the analysis of three large US cohorts showed no evidence of an association of alcohol consumption amount or frequency with PE risk [47]. These findings suggest that alcohol drinking is not a risk factor for VTE.

7. Factors associated with carcinogenesis

The accumulation of various genetic abnormalities in normal cells causes carcinogenesis. Some cancers are caused by congenital genetic abnormalities, but most genetic abnormalities causing cancers are acquired abnormalities. It is estimated that smoking contributes to 20% of cancers and 23% of cancer deaths and infection with helicobacter pylori, hepatitis virus, etc. contributes to 21% of cancers and 22% of cancer deaths in Japanese population, and these are thought to be the main risk factors for cancer in Japanese population. Drinking alcohol contributes to 6% of both cancers and cancer deaths, and it is also a significant risk factor for cancer in Japanese population. Consumption of salt more than 6 g per day, deficiency of fruit intake, and deficiency of vegetable intake also contribute to 1.6, 0.7, and 0.6% of cancers and 1.4, 0.8, and 0.6% of cancer deaths, respectively [48]. Diet and nutrition seem to have some effects on the development of cancer and cancer mortality.

8. Diet, nutrition, and cancer

According to a report “Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective” published by World Cancer Research Fund and American Institute for Cancer Research, it is convincing that adult body fatness has increased risks of esophageal, pancreatic, liver, colorectal, postmenopausal breast, endometrial, and kidney cancer. As for diets and nutrition, there exist causal relationships between aflatoxin and liver cancer, lean and processed meat and colon cancer, arsenic in drinking water and lung cancer, and high-dose beta-carotene supplements and lung cancer. On the other hand, whole grains and food containing dietary fiber decrease colorectal cancer. Non-starchy vegetables and fruits decrease aerodigestive cancer and some other cancers [49]. It is not fully understood how each diet and nutrition has effects on carcinogenesis, a diet with enough vegetables and fruits, less lean and processed meat, reduced carbohydrate and fat to prevent obesity, and low in salt might be useful to reduce cancer incidence.

9. Alcohol, cigarette smoking, and cancer

In 2017, the American Society of Clinical Oncology announced that alcohol drinking had been established as a risk factor for cancer, and avoiding excessive

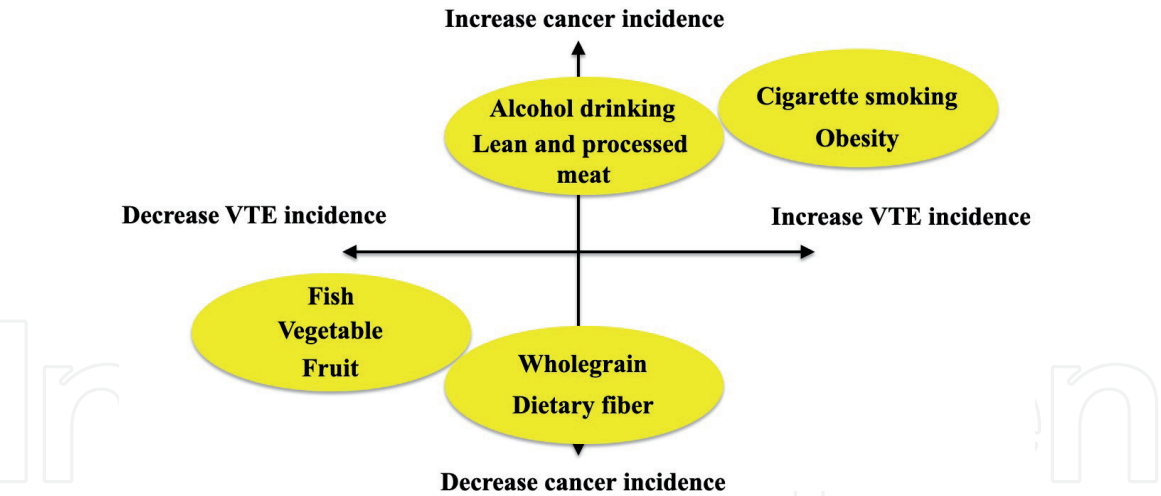


Figure 2.
Effects of diets and lifestyle on cancer and venous thromboembolism (VTE). Fish, vegetables, and fruits may decrease the incidences of both cancer and VTE. Cigarette smoking and obesity increase the incidences of both cancer and VTE. Drinking alcohol and consuming lean and processed meat increase the incidence of cancer. Whole grain and dietary fiber decrease the incidence of cancer.

drinking was important to prevent cancer [50]. The development of pharyngeal, laryngeal, esophageal, liver, breast, and colorectal cancer was obviously related to alcohol drinking. The incidence of esophageal cancer was 1.3 times higher for small drinkers, 2.2 times for moderate drinkers, and 5 times for heavy drinkers than non-drinkers. Ethanol itself is not carcinogenic, but acetaldehyde, its metabolite, binds to DNA and proteins to be carcinogenic and mutagenic. It is proven that administration of large amount of ethanol or acetaldehyde causes cancer in animal experiments [51]. Acetaldehyde is metabolized by aldehyde dehydrogenase 2 (ALDH2). Higher percentage of Japanese people has inactive form of ALDH2 compared to the Western. It might result in adverse effects of alcohol drinking on carcinogenesis in Japanese population.

Smoking is a well-known risk factor for cancer. The International Agency for Research on Cancer (IRAC) assessed causal relationships in 2009 and stated that smoking is related to oral, pharyngeal, laryngeal, esophageal, lung, gastric, colon, liver, pancreatic, renal cell, renal pelvis, ureter, bladder, cervical, and ovarian cancer and chronic myelogenous leukemia. Passive smoking is a risk factor for lung cancer [52]. To prevent cancer of yourself, your family, and your colleagues, no smoking is mandatory (**Figure 2**).

10. Aspirin and cancer

Aspirin is a widely used antiplatelet drug that inhibits platelets' cyclooxygenase (COX), resulting in decreased platelet aggregation. Numerous studies have demonstrated the effects of aspirin on the secondary prevention of arterial thrombosis, and several studies have investigated the effects of aspirin use for the primary prevention of atherosclerotic diseases. Meta-analyses of these studies have shown that daily regular aspirin use reduce the incidence of colon cancer, mortality of colon cancer, and metastasis of colon cancer. The incidence or mortality of other types of cancer might also be reduced [53–55]. Increased COX expression results in tumor growth and progression, and inhibition of COX reduces carcinogenesis in animal experiments. Platelets are known to play an important role in tumor metastasis [56]. These might be related to the inhibitory effects of aspirin on cancer reported in meta-analyses. On the other hand, some recent reports have shown that

Representative reports of large-scale meta-analysis		
Outcome	HR	Reference
Incidence of colon cancer	0.76(0.60 – 0.96)	[53]
Death due to colon cancer	0.65(0.48 – 0.88)	[53]
Death due to cancer	0.79(0.68 – 0.92)	[54]
Cancer with distant metastasis	0.64(0.48 – 0.84)	[55]
Recent publications		
Outcome	HR	Reference
Incidence of cancer	1.24(1.06 – 1.46)	[57]
Death due to cancer	1.08(0.85 – 1.38)	[57]
Death due to cancer	1.31(1.10 – 1.56)	[58]
Incidence of cancer	1.01(0.92 – 1.11)	[59]
HR: Hazard ratio (aspirin vs placebo or no-aspirin).		

Table 3.
Effects of aspirin on cancer incidence and cancer mortality.

regular aspirin use does not decrease cancer incidence or cancer mortality [57–59] (**Table 3**). Further studies are needed to confirm the effects of aspirin on cancer incidence and cancer mortality.

11. Conclusion

Various factors are involved in carcinogenesis and occurrence of cancer-associated VTE. Certain diets and nutrition may reduce the risk of VTE. Some lifestyles may reduce cancer incidence, and other lifestyles increase the risk of cancer. Further studies are needed to create ideal diet, nutrition, and lifestyle to reduce the risk of cancer and cancer-associated VTE.

Conflict of interest

The author declares no conflict of interest.

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